Please type a plus sign (+) inside this box ☐ [+] 12-26-07

PTO/SB/21 (6-99)
Approved for use through 09/30/2000. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.



# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Application Number | 09/997,614 |
| Filing Date | November 15, 2001 |
| First Named Inventor | David BOTSTEIN |
| Group/Art Unit | 1647 |
| Examiner Name | WEGERT, SANDRA L. |
| Total Number of Pages in This Submission: 36 +Append-dix 1-140 | Attorney Docket Number: 39780-2730 P1C29 |

**ENCLOSURES** *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Response
  - ☐ After Final
  - ☐ Version With Markings Showing Changes
  - ☐ Affidavits/declaration(s)
- ☒ **EXTENSION OF TIME REQUEST (2-MONTHS)**
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
  - ☐ Copy of Notice
- ☐ Copy of an Assignment
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- ☐ Terminal Disclaimer
- ☐ Small Entity Statement
- ☐ Request for Refund
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ **APPEAL COMMUNICATION TO GROUP** ***(Appeal Notice, Brief, Reply Brief) (35 pages)***
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ **ADDITIONAL ENCLOSURE(S)** ***(PLEASE IDENTIFY BELOW):***
- ☒ **EVIDENCE APPENDIX 1-140; and POSTCARD**

Remarks

**AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT 08-1641 FOR ANY FEES DUE IN CONNECTION WITH THIS PAPER, REFERENCING ATTORNEY'S DOCKET NO. 39780-2730 P1C29.**

**SIGNATURE OF APPLICANT, ATTORNEY OR AGENT**

| | | | |
|---|---|---|---|
| Firm *or* Individual name | **HELLER EHRMAN LLP** | **SAM L. NGUYEN (Reg. No. 52,496)** | |
| | **275 Middlefield Road, Menlo Park, California 94025** | **Telephone: (650) 324-7000** | **Facsimile: (650) 324-0638** |
| Signature | Sam Nguyen | | |
| Date | **DECEMBER 21, 2007** | Customer Number: | **35489** |

**CERTIFICATE OF EXPRESS MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated below and addressed to: **MAIL STOP Appeal Brief,** Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450, on this date: **December 21, 2007.**

Express Mail Label **EV 581 477 689 US**

| | | | |
|---|---|---|---|
| Typed or printed name | **Dianna Diaz** | | |
| Signature | Dianna Diaz | Date | **December 21, 2007** |

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop ___, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: | Examiner: Wegert, Sandra |
| David BOTSTEIN, et al. | Art Unit: 1647 |
| Application Serial No. 09/997,614 | Confirmation No: 7398 |
| Filed: November 15, 2001 | Attorney's Docket No. 39780-2730 P1C29 |
| For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME** | **Customer No. 35489** |

**EXPRESS MAIL LABEL NO.: 581 477 689 US**
**DATE MAILED: DECEMBER 21, 2007**

**ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES**

**APPELLANTS' BRIEF**

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Action mailed on March 21, 2007. A Response was filed July 23, 2007 and a Notice of Appeal was filed August 21, 2007. An Advisory Action was mailed September 5, 2007. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case. A request for a two month extension of time is filed concurrently herewith.

The following constitutes the Appellants' Brief on Appeal.

## I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Serial No. 09/941,992 recorded November 16, 2001, at Reel 012176 and Frame 0450.

## II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO1097". There exist two related patent applications, (1) U.S. Serial No. 09/997,628, filed November 15, 2001 (containing claims directed to antibodies to the PRO1097 polypeptide), and (2) U.S. Serial No. 09/989,723, filed November 19, 2001 (containing claims directed to nucleic acids encoding PRO1097 polypeptides). These two related applications are also under final rejection from the same Examiner and based upon the same outstanding rejection, therefore appeal of these final rejections are being pursued independently and concurrently herewith.

## III. STATUS OF CLAIMS

Claims 1-118 and 127-128 have been canceled.

Claims 119-126 and 129-131 are in this application.

Claims 119-126 and 129-131 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims in the present Appeal is provided in Section VIII.

## IV. STATUS OF AMENDMENTS

A summary of the prosecution history for this case is as follows:

Previously, in response to a Final Office Action, an Appeal Brief was filed on August 22, 2005. Thereafter, an RCE Response with additional references and affidavits supporting Appellants' arguments was filed July 5, 2006. This Appeal Brief is filed in response to the Final Office Action mailed on March 21, 2007 and the Advisory Action mailed September 5, 2007.

No claim amendments have been submitted after the Final Response of July 23, 2007.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to an isolated polypeptide comprising the amino acid sequence of the polypeptide of SEQ ID NO: 349, referred to in the present application as "PRO1097." The PRO1097 gene was shown for the first time in the present application to be significantly amplified in human lung or colon cancers as compared to normal, non-cancerous human tissue controls (Example 170). This feature is specifically recited in claim 124, and carried by all claims dependent from claim 124. In addition, the invention also claims the amino acid sequence of the polypeptide of SEQ ID NO: 349, lacking its associated signal-peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044 (Independent Claim 124 and dependent Claims 125-126 and 129). The invention is further directed to polypeptides having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO: 349; the amino acid sequence of the polypeptide of SEQ ID NO: 349, lacking its associated signal peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044, wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumor (Independent Claims 119-123). The invention is further directed to a chimeric polypeptide comprising one of the above polypeptides fused to a heterologous polypeptide (Claim 130), and to a chimeric polypeptide wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (Claim 131).

The amino acid sequence of the native "PRO1097" polypeptide (Independent Claims 119-124) and the nucleic acid sequence encoding this polypeptide (referred to in the present application as "DNA59841-1460") are shown in the present specification as SEQ ID NOs: 349 and 348, respectively, and in Figures 244 and 243, respectively found on pages 299, lines 30-34. A full-length PRO1097 polypeptide having the amino acid sequence of SEQ ID NO:349 is described in the specification at, for example, on pages 218-220, line 30 onwards and the isolation of cDNA clones encoding PRO1097 of SEQ ID NO:349 is described in Example 107, page 489 of the specification. The specification discloses that various portions of the PRO1097 polypeptide possess significant sequence similarity to the glycoportease family of proteins and the acyltransferase ChoActase/COT/CPT family (see, for example, page 218, lines 31-34).

PRO polypeptide variants having at least about 80-99% amino acid sequence identity with a full length PRO polypeptide sequence, or a PRO polypeptide sequence lacking the signal peptide are described in the specification at, for example, page 305, line 23 onwards, and percent amino acid sequence identity determination is described at, for example, pages 306-308, line 14 onwards (Independent Claims 119-123). The preparation of chimeric PRO polypeptides (claims 130 and 131), including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 374, lines 24 to page 375, line 9. Examples 140-143 and page 376, line 12 onwards describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

Finally, Example 170, in the specification at page 539, line 19, to page 555, line 5, sets forth a 'Gene Amplification assay' which shows that the PRO1097 gene is amplified in the genome of certain human lung or colon cancers (see Table 9, page 550). The profiles of various primary lung and colon tumors used for screening the PRO polypeptide compounds of the invention in the gene amplification assay are summarized on Table 8, page 546 of the specification.

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 119-126 and 129-131 satisfy the utility/ enablement requirement under 35 U.S.C. §101/112, first paragraph.

2. Whether Claims 119-126 and 129-131 satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

## VII. ARGUMENTS

***Summary of the Arguments***

Issue 1: Utility/ Enablement

Appellants submit that patentable utility for the PRO1097 polypeptides is based upon the gene amplification data for the gene encoding the PRO1097 polypeptide. The specification discloses that the gene encoding PRO1097 showed significant amplification, ranging from 2.313 to 2.346 fold in two different lung primary tumors and 2.114 to 2.532 fold in three different colon primary tumors. Appellants have submitted, with their Brief filed August 22, 2005, a

Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Further, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed August 3, 2004) collectively teach that in general, gene amplification increases mRNA expression.

Second, the Declarations of Dr. Paul Polakis (Polakis I made of record in Appellants' Response filed August 3, 2004, and Polakis II made of record in Appellants' Response filed July 5, 2006), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is good correlation between mRNA levels and polypeptide levels.

In addition, Appellants have filed more than hundred references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques, including gene amplification and microarray. Regardless of the techniques employed, by and large, increased genes/ transcripts levels mostly correlated with increased protein levels, even if accurate predictions of proteins could not be made. The discussions within the Preliminary Amendment filed July 5, 2006, and the arguments therein are hereby incorporated by reference for brevity. While Appellants acknowledge that, in certain instances, DNA/mRNA and protein levels do not correlate, as discussed throughout prosecution, the law does not require the existence of a "necessary" correlation between DNA/mRNA and protein levels, or that protein levels be "accurately predicted". In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the "more likely than not standard".

Appellants submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede to), a

polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Appellants' Response filed August 3, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Appellants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "**there is a strong correlation between mRNA levels and protein expression**, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Appellants submit that, likewise, in the instant application, the Examiner has not presented any evidence specific to the PRO1097 polypeptide to refute Applicant's assertion of a correlation between DNA levels, mRNA levels and protein expression. Appellants add that even though the instant application does not depend on the microarray assay for utility, the facts pertinent to the Decision on Appeal No. 2006-1469 relate to the instant case as well, because the Decision acknowledges that there is a strong correlation between mRNA levels and protein expression.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Ornfoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the teachings in the art, the Polakis Declarations, the widespread data from the use of array chips, etc., one skilled in the art would agree that in most cases if not all, gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data presented for the PRO1097 gene that the PRO1097 polypeptide is also concomitantly overexpressed. Thus it would follow that the claimed PRO1097 polypeptides have utility in the diagnosis of cancer.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO1097 polypeptides. In addition, one of ordinary skill in the art would also

understand how to make and use the recited antibodies for the diagnosis of lung or colon cancer without any undue experimentation.

Issue 2: Written Description

Appellants note that Claims 119-123 recite the structural feature, namely, 80% sequence identity to SEQ ID NO:349, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in lung or colon tumors. The specification provides detailed guidance as to how to identify polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:349 (PRO1097), as well as detailed protocols for determining whether a gene encoding a variant PRO1097 protein is amplified in lung or colon or tumor. Thus one of skill in the art could easily identify whether a variant PRO1097 sequence falls within the parameters of the claimed invention.

As discussed in detail below, whether the Appellants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. **The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.** In fact, based on the detailed description of the cloning and expression of variants of PRO1097 in the specification, the detailed description of the gene amplification assay (Example 170), the description of testing for variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO:349 and the functional recitation in the instant claims, one of skilled in the art would know that Appellants possessed the invention as claimed in the instant claims, at the time of filing of the application. From the specific activity of the claimed polypeptide, the description of the claimed genus is achieved.

Accordingly, a description of the claimed genus has been achieved by the recitation of both structural and functional characteristics.

***Response to Rejections***

**ISSUE 1. Claims 119-126 and 129-131 are supported by a credible, specific and substantial asserted utility, and thus meet the utility requirement of 35 U.S.C. § 101/ 112, first paragraph**

The sole basis for the Examiner's rejection of Claims 119-126 and 129-131 under this section is that the data presented in Example 170 of the present specification is allegedly insufficient under the present legal standards to establish a patentable utility under 35 U.S.C. § 101 for the presently claimed subject matter.

Claims 119-126 and 129-131 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Appellants strongly disagree and, therefore, respectfully traverse the rejection.

**A. The Legal Standard For Utility Under 35 U.S.C. § 101**

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

---

[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

---

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

**B. Proper Application of the Legal Standard**

Appellants respectfully submit that the data presented in Example 170 starting on page 539 of the specification of the specification and the cumulative evidence of record, which underlies the current dispute, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Example 170 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 546). The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 548, lines 33-34). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29) and also, no-template controls (page 548, lines 33-34). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on page 539, lines 37-39. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on . Using this PCR-based assay, Appellants showed that the gene encoding for PRO1097 was amplified, that is, it showed approximately 1.21- 1.23 ΔCt units for lung tumors and 1.08-1.34 ΔCt units for colon tumors which corresponds to $2^{1.21}$ -$2^{1.23}$- fold amplification in lung and $2^{1.08}$ -$2^{1.34}$- fold amplification in colon tumors respectively, or

[17] M.P.E.P. §2107 II (B)(1).

**2.313 to 2.346 fold** in two different lung primary tumors and **2.114 to 2.532 fold** in three different colon primary tumors.

As evidence that the "increase in DNA" in the gene amplification assay is significant, Appellants submitted a Declaration by Dr. Audrey Goddard (with Appeal Brief dated August 22, 2005). The Declaration by Dr. Audrey Goddard provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay.

Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the 2.313 to 2.346 fold in two different lung primary tumors and 2.114 to 2.532 fold in three different colon primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further Appellants submit that the fact that two lung tumor samples and three colon tumor samples tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers, which may not give a positive hit with most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO1097 gene is amplified in two lung/ three colon tumors or in most tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the

amplification data for PRO1097 is significant is what lends support to its usefulness as a tumor marker. It was well known in the art at the time of filing of the application that gene amplification, which occurs in most solid tumors like lung and colon cancers, is generally associated with poor prognosis. Therefore, the PRO1097 gene becomes an important diagnostic marker to identify such malignant lung or colon cancers, even if the malignancy associated with PRO1097 molecule is a rare occurrence. Accordingly, the present specification clearly discloses enough evidence that the gene encoding the PRO1097 polypeptide is significantly amplified in certain types of lung or colon tumors and is therefore, a valuable diagnostic marker for identifying certain types of lung or colon cancers.

Yet the Examiner maintains that "the PRO1097 gene has not been associated with tumor formation or development of cancer.....all that the specification does is present evidence that the DNA encoding PRO1097 is amplified in small number of samples" (Page 5 of the Final Office Action dated March 21, 2007). The Examiner once again relies on the teachings of Pennica *et al.* and Hu *et al.*, to allege that, strong opposing evidence exists regarding the prediction of protein expression from corresponding mRNA levels.

Appellants strongly disagree. Appellants submit that the Examiner applied an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellants.

Further, as has been argued throughout prosecution, it is not a legal requirement to establish a "necessary" correlation between an increase in gene copy number and protein expression levels or to find evidence that protein levels can be accurately predicted from gene amplification data. Accordingly, the question is rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation between gene amplification levels and protein levels. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants have already discussed the references Pennica *et al.* and Hu *et al.* in great detail throughout prosecution and in their Response dated January 5, 2007; these discussions and

arguments are hereby incorporated by reference. Briefly, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. But, the fact that in the case of closely related molecules, there seemed to be no correlation between gene amplification and the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed above, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general.

Regarding Hu, Appellants respectfully submit that the cited Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO1097 molecule. The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different statistical methods*" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency

of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature " using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect *a bias in the literature* to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions are not based on genes/mRNA *in general.*

Therefore, Appellants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of *one* class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore, when the proper legal standard is used, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.* or Hu *et al.* by the Examiner.

Appellants also submit that Example 170 in the specification clearly discloses that, "(a)mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung,

breast and other cancers and diagnostic determination of the presence of those cancers" (emphasis added). Besides, Appellants have submitted ample evidence (discussed below) to show that, in general, if a gene is amplified in cancer, it is "more likely than not" likely that the encoded protein will also be expressed at an elevated level.

For support, Appellants presented the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed August 3, 2004), who collectively teach that in general, for most genes, DNA amplification increases mRNA expression. The results presented by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* are based upon wide ranging analyses of a large number of tumor associated genes. Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Also, the Declarations of Dr. Paul Polakis (made of record in Appellants' Response filed August 3, 2004 (Polakis I) and July 5, 2006 (Polakis II), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles. Appellants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. For instance, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In

approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his Declarations, show that, in general, there is good correlation between , mRNA levels and polypeptide levels.

Appellants further submitted more than 100 references presented in the IDS of July 5, 2006 and maintain that, both Polakis Declarations (Polakis I and II) and the teachings in the art, support Appellants' assertion, in general, that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Appellants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Appellants' asserted utility, a person of skill in the art would conclude that Appellants' asserted utility is "more likely than not true." *Id.*

Moreover, Appellants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "**there is a strong correlation between mRNA levels and protein expression**, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Appellants submit that, likewise, in the instant application, the Examiner has not presented any evidence specific to the PRO1097 polypeptide to refute Applicant's assertion of a correlation between DNA levels, mRNA levels and protein expression. Appellants add that even though the instant application does not depend on the microarray assay for utility, the facts pertinent to the Decision on Appeal No. 2006-1469 relate to the instant case as well, because the Decision acknowledges that there is a strong correlation between mRNA levels and protein expression.

Taken together, all of the submitted evidence supports the Appellants' position that, in the majority of amplified genes, increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels, which clearly meets the utility standards described above. Hence, one of skill in the art would reasonably expect that, based on the gene amplification data of the PRO1097 gene, the PRO1097 polypeptide is concomitantly overexpressed in the lung or colon tumors studied as well.

Appellants further submit that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not

concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Appellants' Response filed August 3, 2004) explains:

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Thus, even if over-expression of the gene product does not parallel gene amplification in certain tumor types, parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999), submitted with the Response filed August 3, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In this rejection, the Examiner further relies on the teachings of Bieche *et al.* and Pitti *et al.* to allege that these authors did not use their data for diagnostic purposes, as in the instant application.

Appellants respectfully submit that the references Bieche *et al.* and Pitti *et al.* were first submitted by Appellants in the Goddard Declaration as Exhibits F and G. These references were presented to demonstrate the validity of use of the negative control *i.e.,* the "pooled normal blood controls" as control, which is the control used in the gene amplification assay described in the

instant application. The pooled DNA sample control was widely utilized and accepted as a true negative control as demonstrated by use in peer reviewed publications, for instance, in Bieche *et al.* and Pitti *et al.* For example, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay described in the specification to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. As described, Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1; Emphasis added). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2), thus confirming the validity of the negative control.

However, the Examiner cites these references in the Final Office action to show that Bieche *et al.* and Pitti *et al.* did not use their data for (cancer) diagnostic purposes. Appellants respectfully disagree with the context in which the Examiner makes her interpretation. The fact that Bieche *et al.* and Pitti *et al.* used the pooled blood sample as a negative control in a gene amplification assay is of significance. That Bieche *et al.* and Pitti *et al.* did not use these controls for diagnostic purposes should bear no consequence to the utility for the instant application. Accordingly, the Examiner has not presented valid arguments or contrary evidence to show that the pooled control was not acceptable at the time of filing. Such a rejection is therefore improper.

The Examiner maintains that "the specification provides data purportedly showing a slight increase in DNA copy number in two different types of tumor tissue (lung and colon) of PRO1097" and further alleges that "gene amplification does not reliably correlate with polypeptide over-expression." The Examiner acknowledges that PRO1097 is novel but alleges "it is not known whether PRO1097 is expressed in corresponding normal tissues and what the relative levels of expression are." The Examiner adds that she "cannot find any reason to suspect, that the protein encoded by the PRO1097 gene would confer any selective advantage on

a cell expressing it" and that "the instant specification does not teach structure/ function analysis." (Page 3 of the Final Office Action dated March 21, 2007).

Once again, Appellants point out that using the PCR-based assay, Appellants made the assertion that the gene encoding for PRO1097 was significantly amplified. The Declaration by Dr. Audrey Goddard explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample, relative to a normal sample, is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. The Examiner requests "structure/ function data" in the Office Action, but Appellants respectfully remind the Board that this is not a requirement for the utility requirement. Further, the Examiner asks Appellants to show "that the protein encoded by the PRO1097 gene would confer any selective advantage on a cell expressing it." That is, the Examiner requests Appellants to show the mechanism by which the claimed protein acts within the cell. Appellants believe that such a requirement is a heightened utility standard imposed by the Examiner. The mechanism of action need not be understood for attaining that utility. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)." Thus, Appellants submit that such a concern is misplaced, and cannot properly form the basis of the rejections of the present claims.

Appellants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1097 polypeptide of SEQ ID NO:349 and that the increase in gene amplification for the DNA encoding PRO1097 is sufficient to confer patentable utility to the instantly claimed PRO1097 polypeptides, for the reasons presented throughout the prosecution of this application. Appellants add that the gene amplification data clearly supports a role for PRO1097 as a lung or colon tumor marker.

Thus, based on the asserted utility for PRO1097 in the diagnosis of selected lung or colon tumors, the reduction to practice of the instantly claimed protein sequence of SEQ ID NO: 349 in the present application (also see page 305), the disclosure of the step-by-step protocols for making chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an

epitope tag or an Fc region of an immunoglobulin in the specification (at page 374, lines 24 to page 375, line 9), the disclosure of a step-by-step protocol for making and expressing PRO1097 in appropriate host cells (in Examples 140-143 and page 376, line 12), the step-by-step protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO1097 protein in the specification (at pages 390-395) and the disclosure of the gene amplification assay in Example 170, the skilled artisan would know exactly how to make and use the claimed polypeptide for the diagnosis of lung or colon cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue'.

Therefore, since the instantly claimed invention is supported by either a credible, specific and substantial asserted utility or a well-established utility, and since the present specification clearly teaches one skilled in the art "how to make and use" the claimed invention without undue experimentation, Appellants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §101 and §112, First Paragraph to Claims 119-126 and 129-131.

**ISSUE 2: Claims 119-126 satisfy the written description requirement of 35 U.S.C. §112, First Paragraph**

Claims 119-126 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner has asserted that "Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 349, while retaining the function of SEQ ID NO: 349." The Examiner adds that allegedly, Appellants have not "described a representative number of species that have 80-99% homology to SEQ ID NO: 349, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 349" (Page 10 of the Final Office Action mailed March 21, 2007).

Appellants respectfully disagree.

## A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[18,19] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[20] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[21,22]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[23], the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."[24] Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[25,26]

---

[18] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[19] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[20] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[21] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[22] *See also* M.P.E.P. §2163 II(A).

[23] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[24] *See also* M.P.E.P. §2141.03.

[25] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[26] See *also* M.P.E.P. §2141.03.

**B. The Disclosure Provides Sufficient Written Description for the Claimed Invention**

As discussed above, whether the Appellants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. **The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.**

The currently amended claims are directed to the genus of nucleic acids encoding polypeptides with at least 80-99% sequence identity to SEQ ID NO: 349 with the functional recitation: "wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer," which, as discussed above, is based on **a well-established assay known to the skilled artisan at the effective filing date of this application**. Moreover, the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO: 349, with or without its signal sequence, or encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044. Therefore, the claimed polypeptides of Claims 119-123 and their dependents are defined both by functional as well as structural features. Based on the detailed description of the cloning and expression of variants of PRO1097 in the specification, the detailed description of the gene amplification assay (Example 170), the description of testing for variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO:349 and the functional recitation in the instant claims, one of skilled in the art would know that Appellants possessed the invention as claimed in the instant claims, at the time of filing of the application. From the specific activity of the claimed polypeptide, the description of the claimed genus is achieved.

As described before during prosecution, Appellants submit that the specification provides ample written support for determining percent sequence identity between two amino acid sequences (See pages 306-308, line 14 onwards). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 372, line 36 to page 373, line 17). This

guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Accordingly, one of skill in the art could identify whether the variant PRO1097 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 376, line 9) and methods of preparing the PRO polypeptides (see Example 140-143).

The current specification also provides ample written support for detecting and quantifying amplification of nucleic acids in several tumors and/or cell lines as described in Example 170. Example 170 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following this disclosure, one skilled in the art would know that it is easy to test whether a gene encoding a variant PRO1097 protein is amplified in lung or colon tumors by the methods set forth in Example 170.

Thus, the genus of polypeptides with at least 80-99% sequence identity to SEQ ID NO: 349, which possess the functional property of having a nucleic acid which is amplified in lung or colon tumor would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description. Accordingly, one skilled in the art would have known that Appellants had knowledge and possessed the claimed polypeptides with 80-99% sequence identity to SEQ ID NO: 349 whose encoding nucleic acids were amplified in lung or colon tumors. The recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand.

For the above reasons, the specification provides adequate written description for polypeptides having at least 80% identity to SEQ ID NO: 349 wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumor. Accordingly, Appellants respectfully request reconsideration and reversal of the written description rejection of Claims 119-126 under 35 U.S.C. §112, first paragraph.

## CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification

clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of claims 119-126 and 129-131.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C29**.

Respectfully submitted,

Date: December 21, 2007

By: _____
Sam L. Nguyen (Reg. No. 52,496)
on behalf of Daphne Reddy (Reg. No. 53,507)

**HELLER EHRMAN LLP**
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

## VIII. CLAIMS APPENDIX

**Claims on Appeal**

119. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:349;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:349, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer.

120. An isolated polypeptide having at least 85% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:349;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:349, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer.

121. An isolated polypeptide having at least 90% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:349;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:349, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer.

122. An isolated polypeptide having at least 95% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:349;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:349, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer.

123. An isolated polypeptide having at least 99% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:349;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:349, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer.

124. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 349;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 349, lacking its associated signal peptide;

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon cancer.

125. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 349.

126. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 349, lacking its associated signal peptide.

129. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203044.

130. A chimeric polypeptide comprising a polypeptide according to Claim 124 fused to a heterologous polypeptide.

131. The chimeric polypeptide of Claim 130, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

## IX. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:

   A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
   B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
   C. Livak, K.J., *et al.*, "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* 4:357-362 (1995).
   D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
   E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
   F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
   G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).

3. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis I).

4. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis II).

5. Hyman, E., *et al.*, "Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002).

6. Pollack, J.R., *et al.*, "Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002).

7. Hanna *et al.*, "HER-2/neu Breast Cancer Predictive Testing," Pathology Associates Medical Laboratories (1999).

8. Hu *et al.*, "Analysis of genomic and proteomic data using advanced literature mining" *J. Proteome Res.* 2: 405-412 (2003).

9. Abe, N., *et al.*, Br J Cancer - 89(11):2104-9 (2003).

10. Alberts, B., *et al.*, Molecular Biology of the Cell (3rd ed. 1994) Cell 3rd at 453 Figure 9-2 of Cell 3rd Cell 3rd at 403.

11. Alberts, B., *et al.*, Molecular Biology of the Cell (4rd ed.) In Cell 4th, Figure 6-3 on page 302 Figure 6-90 on page 364 of Cell 4th Cell 4th at 364 Cell 4th at 379.

12. Ando, M., *et al.*, Br J Haematol., - 130(6):860-8 (2005).

13. Aust, G., *et al.,* Thyroid - 7(5):713-24 (1997).

14. Barnes, V.L., *et al.,* J Histochem Cytochem. - 47(6):787-98 (1999).

15. Bea, S., *et al.,* Cancer Res. - 61(6):2409-12 (2001).

16. Beer, *et al.,* Nature Medicine - 8(8):816-824 (2002).

17. Blaschke, V., *et al.,* J Immunol Methods. - 246(1-2):79-90 (2000).

18. Buckley, A.R., *et al.,* Apoptosis. - 2(6):518-28 (1997).

19. Caberlotto, L. *et al.,* Neurosci Lett. - 265(3):191-4 (1999).

20. Caberlotto, L., *et al.,* Eur J Neurosci. - 17(9):1736-46 (2003).

21. Choi, D., *et al.,* J Soc Gynecol Investig. - 9(1):41-6 (2002).

22. Couvelard, A., *et al.,* Virchows Arch. - 445(3):279-84 (2004).

23. Dagenais, A., *et al.,* Am J. Physio Lung Cell Mol Physiol. - 286(2):L301-11 (2004).

24. De Boer, C.J., *et al.,* Ann Oncol. - 7(3):251-6 (1996).

25. Debieve, F., *et al.,* Mol Hum Reprod. - 6(8):743-9 (2000).

26. Dong, Z., *et al.,* Invest Opthalmol Vis Sci - 42(13):3223- (2001).

27. Duchrow, M., *et al.,* Cancer Invest. - 19(6):588-96 (2001).

28. Dyer, J., *et al.,* Equine Vet J. - 34(4):349-58 (2002).

29. Egwuagu, C.E., *et al.,* J Immunol. - 168(7):3181-7 (2002).

30. El-Ghrably, I.A., *et al.,* Br J Opthalmol. - 85(4):461-70 (2001).

31. Eleore, L., *et al.,* Neuroscience - 136(1):147-60 (2005).

32. Forsberg, H., *et al.,* Free Radic Res. - 24(6):451-9 (1996).

33. Freyschuss, B., *et al.,* Endocrinology - 133(4):1548-54 (1993).

34. Fu, K., *et al.,* Blood - 106(13):4315-21 (2005).

35. Fuchs, A.R., *et al.,* Biol Reprod. - 54(3):700-8 (1996).

36. Furuta, J., *et al.,* Melanoma Res. - 15(1):15-20 (2005).

37. Futcher, B., *et al.,* Mol Cell Biol., - 19(11):7357-68 (1999).

38. George, J., *et al.,* Biochem Pharmacol. - 49(7):873-81 (1995).

39. Giroux, M., *et al.,* J Immunol. - 165(7):3985-91 (2000).

40. Gnatenko, D.V., *et al.,* Blood - 101(6):2285-93 (2003).

41. Godbout, R., *et al.,* J Biol Chem, - 273(33):21161-8 (1998).

42. Goldenberg, R.C., *et al.,* J Endocrinol. - 177(2):327-35 (2003).

43. Golebiowski, F., *et al.,* Acta Biochim Pol. - 50(4):1065-73 (2003).

44. Greenbaum, D., *et al.,* BioinformaticsI - 18(4):585-496 (2002).

45. Grem, J.L., *et al.,* Clin Cancer Res. - 7(4):999-1009 (2001).

46. Grenback, E., *et al.,* Regul Pept, - 117(2):127-39 (2004).

47. Gromova, I., *et al.,* Int J. Oncol. - 13(2):379-83 (1998).

48. Guo, Y., *et al.,* Zhinghua Jie He He Hu Xi Za Zhi - 25(6):337-40 (2002).

49. Habu, Y., *et al.,* Biochem Pharmacol - 69(6):993-9 (2005).

50. Hahn, M.E., *et al.,* Toxicol Appl Pharmacol. - 127(2):187-98 (1994).

51. Hähnel, E., *et al.,* Breast Cancer Research and Treatment - 24:71-74 (1992).

52. Hamilton, L.M., *et al.,* Clin Exp Allergy. - 33(2):233-40 (2003).

53. Hassett, C., *et al.,* Arch Biochem Biophys. - 337(2):275-83 (1997).

54. Hirsch, F.R., *et al.,* Clinical Cancer Research - 7:5-22 (2001).

55. Holten-Andersen, M.N., *et al.,* Int J Cance, - 113(2):198-206 (2005).

56. Huang, Y.H., *et al.,* J Med Virol. - 70(4):610-6 (2003).

57. Huettner, P.C., *et al.,* Mod Pathol. - 5(3):250-6 (1992).

58. Hui, P., *et al.,* Leuk Lymphoma. 44(8):1385-94 (2003).

59. Husain, I., *et al.,* Cancer Res. - 54(2):539-46 (1994).

60. Ihmann, T., *et al.,* J Cancer Res Clin Oncol. - 130(12):749-56 (2004).

61. Ikegami, T., *et al.,* Am J Physiol Cell Physiol. - 281(4):C1396-402 (2001).

62. Jacquemin, E., *et al.,* Int J Biol. - 37(3):417-23 (1993).

63. Jaime, M., *et al.,* Hepatology - 35(5):1063-71 (2002).

64. Janssens, N., *et al.,* Tumour Biol. - 25(4):161-71 (2004).

65. Jungbluth, A.A., *et al.,* Int J. Cancer - 92(6):856-60 (2001).

66. Kalabis, G.M., *et al.,* Biol Reprod. - 73(4):591-7 (2005).

67. Kammaori, M., *et al.,* Int J Oncol. - 27(5):1257-63 (2005).

68. Khal, J., *et al.,* Br J Cancer - 93(7):774-80 (2005).

69. Khal, J., *et al.,* Int J. Biochem Cell Biol. - 37(10):2196-206 (2005).

70. Kogo, H., *et al.,* J Biol Chem. - 279(24):25574-81 (2004).

71. Kommoss, F., *et al.,* Acta Obstet Gynecol Scand Suppl. - 155:19-24 (1992).

72. Kumar, U., *et al.,* Breast Cancer Res. Treat. - 92(2):175-86 (2005).

73. Kuo, C.C., *et al.,* Proteomics - 5(4):894-906 (2005).

74. Landmark, B.F., *et al.,* J Reprod Fertil. - 99(2):323-34 (1993).

75. Lassmann, S., *et al.,* J Pathol. - 198(2):198-206 (2002).

76. Legrand, O., *et al.,* Br J, Haematol. - 94(1):23-33 (1996).

77. Lemstrom, K.B., *et al.,* Circulation - 105(21):2524-30 (2002).

78. Lewin, B., Genes VI Genes VI at 847-848 (1997).

79. Li, Y., *et al.,* Invest Ophthalmol Vis Sci. - 44(3):1299-304 (2003).

80. Li, Z.B., *et al.,* Biochem Biophys Res Commun. - 327(4):1163-9 (2005).

81. Lindberg, P., *et al.,* Arch Oral Biol. - 46(1):23-31 (2001).

82. Macabeo-Ong, M., *et al.,* 15(9):979-87 (2002).

83. Maruyama, H., *et al.,* Am J Pathol. - 155(3):815-22 (1999).

84. Meehan, T.P., *et al.,* J Mol Endocrinol. - 32(1):247-55 (2004).

85. Mendoza-Rodriguez, C.A., *et al.,* Mol Reprod Dev. 64(4):379-88 (2003).

86. Meoni, P., *et al.,* Brain Res Mol Res. - 54(1):13-23 (1998).

87. Meric, F., *et al.,* Molecular Cancer Therapeutics - 1:971-979 (2002).

88. Mezzano, S.A., *et al.,* Kiney Int. - 57(1):147-58 (2000).

89. Mingrone, G., *et al.,* Obes Res. - 11(5):632-40 (2003).

90. Miralles, C.P., *et al.,* Brain Res Mol Res. - 24(1-4):129-39 (1994).

91. Mizrachi, D., *et al.,* Biol Reprod. - 61(3):776-84 (1999).

92. Monaghan, P., *et al.,* J Gen Virol. - 86(Pt 10):2769-80 (2005).

93. Montuori, N., *et al.,* Int J Cancer - 105(3):353-60 (2003).

94. Munaut , C.,*et al.,* Int J Cancer - 106(6):848-55 (2003).

95. Nie, Y., *et al.,* Carcinogenesis - 22(10):1615-23 (2001).

96. Nuciforo, P.G., *et al.,* Hum Pathol. - 34(7):639-45 (2003).

97. Oberringer, M., *et al.,* Biochem Biophys Res Commun. - 214(3):1009-14 (1995).

98. Orntoft, T.F., *et al.* Molecular & Cellular Proteomics – 1:37-45 (2002).

99. Pachmann, K., *et al.,* Br J. Haematol - 112(3):749-59 (2001).

100. Pairon, J.C., *et al.,* Am J Respir Cell Mol Biol. - 11(4):386-96 (1994).

101. Papotti, M., *et al.,* Diagn Mol Pathol. - 9(1):47-57 (2000).

102. Papotti, M., *et al.,* Virchows Arch. - 440(5):461-75 (2002).

103. Paredes, J., *et al.,* Clin Cancer Res. - 11(16):5869-77 (2005).

104. Politis, I., *et al.,* J Dairy Sci. - 75(6):1423-9 (1992).

105. Preesman, A.H., *et al.,* J Invest Dermatol. - 99(5):587-93 (1992).

106. Pullig, O., *et al.,* Osteoarthritis Cartilage - 10(4):253-63 (2002).

107. Rey, C., *et al.,* Biochem Pharmacol. - 60(11):1639-46 (2000).

108. Rudlowski, C., *et al.,* Am J. Clin Pathol. - 120(5):691-8 (2003).

109. Sasaki, T., *et al.,* Exp Cell Res. - 275(2):185-99 (2002).

110. Sedelies, K.A., *et al.,*J Biol Chem. - 279(25):26581-7 (2004).

111. Shen, Y., *et al.,* Blood - 104(9):2936-9 (2004).

112. Shinohara, Y., *et al.,* Biochim Biophys Acta - 1368(1):129-36 (1998).

113. Silvers, A.L., *et al.,* Photochem Photbiol. - 75(3):302-10 (2002).

114. Song, L., *et al.,* Am J. Physiol. - 267(4 Pt 2):F546-57 (1994).

115. Spaziani, E.P., *et al.,* J Interferon Cytokine Res. - 18(12):1039-44 (1998).

116. Spika, I., *et al.,* Skin Pharmacol Appl Skin Physiol. - 16(3):143-50 (2003).

117. Splinter, P.L., *et al.,* J Biol Chem - 278(8):6268-74 (2003).

118. Stearns, M.E., *et al.,* Cancer Res. - 53(4):878-83 (1993).

119. Stein, R., *et al.,* J Urol. - 164(3Pt 2):1026-30 (2000).

120. Strickland, I., *et al.,* J Invest Dermatol. - 108(5):763-8 (1997).

121. Strutz, F., *et al.,* Kidney Int. - 57(4):1521-38 (2000).

122. Takahashi, K., *et al.,* J Biol. Chem. - 278(47):46654-60 (2003).

123. Takimoto, Y., *et al.,* Circulation - 105(4):490-6 (2002).

124. Telek, G., *et al.,* J Surg Res. - 96(1):56-67 (2001).

125. Timchenko, L., *et al.,* Semin Cell Biol. - 6(1):13-9 (1995).

126. Torronen, R., *et al.,* Chem Biol. Interact. - 83(2):107-19 (1992).

127. Ullmannova, V., *et al.,* Leuk Res. - 27(12):1115-23 (2003).

128. Van Beers, E.H., *et al.,* J Histochem Cytochem. - 46(2):231-40 (1998).

129. Van Der Wilt, C.L., *et al.,* Eur J Cancer - 39(5):691-7 (2003).

130. Waldherr, R., *et al.,* Pediatr Nephrol. - 7(4):471-8 (1993).

131. Walmer, D.K., *et al.,* Cancer Res. - 55(5):1168-75 (1995).

132. Wang, J., *et al.,* Cancer Res. - 54(2):560-4 (1994).

133. Wang, J., *et al.,* Urol Res. - 28(5):308-15 (2000).

134. Wang, L.G., *et al.,* Cancer Res. - 57(4):714-9 (1997).

135. Weterman, M.A., *et al.,* Cancer Res. - 53(24):6061-6 (1993).

136. Williams, E.T., *et al.,* J Pharmacol Exp Ther. 311(2):728-35 (2004).

137. Wojtaszek, P.A., *et al.,* Oncogene - 8(3):755-60 (1993).

138. Zhigang, Z., *et al.,* World Journal of Surgical Oncology - 2-13 (2004).

139. Zhong, W., *et al.,* Free Radic Biol Med. - 27(11-12):1334-45 (1999).

140. Xi, L., *et al.,* Zhonghua Fu Chan Ke Za Zhi - 40(6):407-10 (2005).

Item 1 was submitted with Appellants' Brief filed August 22, 2005.

Items 2, 3 5-7 and 98 were submitted with Appellants' Response filed August 3, 2004, and were considered by the Examiner as indicated in the Final Office action mailed October 20, 2004.

Items 1(E: Pennica) and item 8 were made of record by the Examiner in the Final Office Action mailed October 20, 2004.

Items 4 and 9-140 were submitted with Appellants' Preliminary Amendment filed July 5, 2006.

## X. RELATED PROCEEDINGS APPENDIX

None- no decision rendered by a Court or the Board in any related proceedings identified above.

SV 2297559 v1